REMARKS

Entry of the enclosed amendments is respectfully requested since they either put the claims in condition for allowance or simplify issues for appeal.

Rejection under §101 and §112, first paragraph

On Page 5 of the Office action, it is stated: "the Specification does not disclose information regarding the nexus between ICSR-1 expression or function and a pathological condition, thus this asserted utility is neither specific nor substantial." This appears to the sole basis for the utility rejection.

"As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. In re Langer, 503 F.2d at 1391, 183 USPQ at 297 (emphasis in original)." M.P.E.P. 2107.02.III.A. The burden is on the examiner to provide a sufficient evidentiary basis for the §101 rejection. See, M.P.E.P. 2107.02.IV.

In the present rejection, the examiner has failed to sustain this burden. No evidence has been presented that one of ordinary in the art would question the disclosed utility as a marker for heart tissue. It is alleged in the Office action that a "nexus between ICSR-1 expression or function and a pathological condition" is necessary to establish utility in view of its tissue-specificity, but not a single legal case or reason has been stated for this position. Rather, the Examiner appears to believe that it is bedrock law that pathology – i.e., disease – is necessary to establish a utility for a tissue specific marker. However, no source for this belief has been provided, nor any reasoned statements for why a connection to a disease state is necessary. Absent this information, the rejection cannot be maintained.

On Page 5 of the Office action, the Examiner argued that Example 12 of the Utility Guidelines was inapplicable to the pending claims. However, the Examiner did not address Applicant's arguments (on the same page of the Response) regarding Example 6 of the Guidelines. This example in the Synopsis of Application of Written Description Guidelines described a "glial specific G-coupled protein receptor whose function is associated with glial differentiation." Indeed, this is an example of specificity for a normal tissue. There is no indication in the example that the claim was deficient on any other statutory ground. If it were, it would have been entirely misleading and disingenuous of the Office not to have brought this to patent practitioners' attention. Nonetheless, Applicant does not wish to stand on this example, for fear of diverting the Examiner from the real issue: the tissue-specificity described for the pending claims is adequate to satisfy §101, and no evidence has been presented to the contrary.

Because a *prima facie* showing that the claimed invention lacks utility has not been established, Applicant is entitled to withdrawal of the rejection and no further argument is necessary. The claimed subject matter's usefulness to detect heart tissue (e.g., Specification, Page 33) must be taken as in compliance with the statutory requirements of §101.

Although unnecessary, attached are several references (Exhibit A) that show that heart tissue specificity is a recognized utility in the art. These references show that heart specific markers are utilized in both clinical and research medicine. For example, the publications illustrate that heart markers are useful for identifying heart tissue in pathology slides, for assessing heart damage, and for determining the differentiation of undifferentiated cells into heart tissue. Additionally, a heart marker can be used as target for labeled antibodies (Specification, Page 16, lines 8-33; Page 20, lines 10-17), e.g., for imaging the heart.

Rejection under §112, first paragraph

The claims were amended in the previous Response by the addition of hybridization language. This format was stated by the Patent Office to conform to the requirements of §112,

first paragraph. The recited hybridization conditions yield structurally similar sequences. See, Synopsis of Written Description Guidelines, Example 9; Enzo Biochem. Inc. v. Gen-Probe Inc., 63 USPQ2d 1609 (Fed. Cir. 2002). Thus, the Examiner's arguments on Pages 6-10 have already been rejected by the Patent Office. As far as the objection on Page 6 (3 lines from the bottom), Page 8 (last line), Page 9 (first line), etc., to the term "variant," it is noted that this term was canceled from the independent claims in the previous Response. It has now been removed from the dependent claims where it inadvertently had not been deleted.

Rejection under §112, second paragraph

The term "specific" has been canceled.

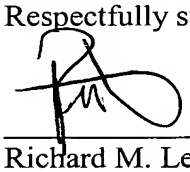
Rejection under §102

Claims 1, 7, and 8 have been amended by incorporating the aspect of dependent Claim 16. Claim 4 has been amended by incorporating the aspect of dependent Claim 12. It is believed that this amendment renders the rejection moot, since neither Claim 12 or 16 were subject to this rejection.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Attorney Docket No.: MERCK-2354

Date: January 26, 2005

1: J Heart Lung Transplant. 2005 Jan;24(1):46-51. Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Simvastatin decreases myocardial tumor necrosis factor alpha content in heart transplant recipients.

Wallace CK, Stetson SJ, Kucuker SA, Becker KA, Farmer JA, McRee SC, Koerner MM, Noon GP, Torre-Amione G.

Baylor College of Medicine, Houston, Texas, USA.

BACKGROUND: Statins improve patient survival and decrease rejection episodes in heart transplant recipients. We studied the effects of simvastatin treatment on myocardial tumor necrosis factor alpha (TNF-alpha) expression; TNF-alpha is a potent pro-inflammatory cytokine associated with hypertrophy and fibrosis in heart transplant recipients. METHODS: We randomized 10 consecutive heart transplant recipients to receive either 20 mg/day simvastatin (n = 5) or placebo (n = 5) for 6 months after cardiac transplantation. Routine surveillance endomyocardial biopsy specimens were obtained from all patients. We analyzed tissues for myocardial TNF-alpha content, total collagen content, and myocyte size using semiquantitative immunohistochemistry. RESULTS: Myocyte size and total collagen content of placebo and simvastatin groups did not show a statistically significant difference at any biopsy time point. Myocardium TNF-alpha content (% tissue area stained) at 1 week after transplantation was similar in the simvastatin and placebo groups. At the 24(th) week after transplantation, when compared with Week 1 values, we found a significant decrease in myocardium TNF-alpha content in the simvastatin group (15.0% +/- 2.3% vs 5.8% +/- 2.4%, p = 0.02) that was not observed in the placebo group (15.0% +/- 1.5% vs 12.0% +/- 2.6%, p = not significant). CONCLUSION: Simvastatin treatment in heart transplant recipients decreased myocardium TNF-alpha expression. This decrease did not translate into a difference in the markers of hypertrophy. However, decreased myocardial TNF-alpha may be a marker of a general statin-mediated decrease in inflammation in the transplanted heart that leads to improved graft and patient survival.

PMID: 15653378 [PubMed - in process]

Upregulation of redox-regulating protein, thioredoxin, in endomyocardial biopsy samples of patients with myocarditis and cardiomyopathies.

Nimata M, Kishimoto C, Shioji K, Ishizaki K, Kitaguchi S, Hashimoto T, Nagata N, Kawai C.

Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

An important role of redox regulation in myocardial diseases and heart failure has been postulated. Thioredoxin (TRX) is a redox-regulating protein. Recent studies indicated a possible association between plasma TRX concentrations and the severity of heart failure. Accordingly, we investigated the myocardial expression of TRX in patients with myocarditis and cardiomyopathies. Four cases of hypertrophic cardiomyopathy (HCM), 10 of dilated cardiomyopathy (DCM), 6 of myocarditis, and 5 of controls were studied. Right and left ventricular endomyocardial biopsy samples were obtained at the diagnostic cardiac catheterization. The samples were processed for immunohistological staining for TRX, which was done by the indirect immunoperoxidase technique. 8-hydoxy-2'-deoxyguanosine (8-OHdG), one of the major DNA base-modified products, was also detected for an established marker for oxidative stress. TRX immunoreactivity was none or trivial in control specimens. Positive TRX staining was found in 6 cases; 3 in active myocarditis and 3 in DCM. The positive staining was found in infiltrating cells and damaged myocytes in the perinecrotic lesions. Damaged myocytes were also positive for 8-OHdG All the 3 cases of DCM positive for TRX stain showed severe left ventricular hypertrophy on electrocardiogram and highly elevated left ventricular end-diastolic pressure (> 24 mmHg), suggesting the overload of oxidative stress by hemodynamic impairment. Myocardial TRX was upregulated in myocarditis and cardiomyopathies with active necrotic stage associated with DNA damage, which may reflect the oxidative stress overload in hemodynamically uncontrolled status.

PMID: 12870673 [PubMed - indexed for MEDLINE]

1: Biochem Biophys Res Commun. 2004 Feb 6;314(2):420-7. Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Differentiation of human adipose tissue stem cells using extracts of rat cardiomyocytes.

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Institute of Medical Biochemistry, University of Oslo, Oslo, Norway.

We report the differentiation of human adipose tissue stem cells (ATSCs) to take on cardiomyocyte properties following transient exposure to a rat cardiomyocyte extract. Reversibly permeabilized ATSCs were incubated for 1h in a nuclear and cytoplasmic extract of rat cardiomyocytes, resealed with CaCl(2), and cultured. Three weeks after exposure to extract, ATSCs expressed several cardiomyocyte markers including sarcomeric alpha-actinin, desmin, and cardiac troponin I, and displayed targeted expression of the gap junction protein connexin 43. Formation of binucleated and striated cells, and spontaneous beating in culture were also observed. A low proportion of intact ATSCs exposed to the extract also showed signs of alpha-actinin and connexin 43 expression. Additional evidence of differentiation was provided by induction of expression of nuclear lamin A/C, a marker of terminally differentiated cells, and a remarkable increase in cell cycle length. Together with our previous data, this study suggests that alteration of cell fate using cellular extracts may be applied to multiple cell types. Cell extracts may also prove useful for investigating the molecular mechanisms of stem cell differentiation.

PMID: 14733922 [PubMed - indexed for MEDLINE]

1: Circulation. 2003 Jun 3;107(21):2733-40. Epub 2003 May 12. Related Articles, Links

Comment in:

- Circulation. 2003 Jun 3;107(21):2638-9.

Differentiation of human embryonic stem cells to cardiomyocytes: role of coculture with visceral endoderm-like cells.

Mummery C, Ward-van Oostwaard D, Doevendans P, Spijker R, van den Brink S, Hassink R, van der Heyden M, Opthof T, Pera M, de la Riviere AB, Passier R, Tertoolen L.

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BACKGROUND: Cardiomyocytes derived from human embryonic stem (hES) cells could be useful in restoring heart function after myocardial infarction or in heart failure. Here, we induced cardiomyocyte differentiation of hES cells by a novel method and compared their electrophysiological properties and coupling with those of primary human fetal cardiomyocytes. METHODS AND RESULTS: hES cells were cocultured with visceral-endoderm (VE)-like cells from the mouse. This initiated differentiation to beating muscle. Sarcomeric marker proteins, chronotropic responses, and ion channel expression and function were typical of cardiomyocytes. Electrophysiology demonstrated that most cells resembled human fetal ventricular cells. Real-time intracellular calcium measurements, Lucifer yellow injection, and connexin 43 expression demonstrated that fetal and hES-derived cardiomyocytes are coupled by gap junctions in culture. Inhibition of electrical responses by verapamil demonstrated the presence of functional alpha1c-calcium ion channels. CONCLUSIONS: This is the first demonstration of induction of cardiomyocyte differentiation in hES cells that do not undergo spontaneous cardiogenesis. It provides a model for the study of human cardiomyocytes in culture and could be a step forward in the development of cardiomyocyte transplantation therapies.

PMID: 12742992 [PubMed - indexed for MEDLINE]